

## Article

# A large Northern European observational study of follitropin alpha filled-by-mass pre-filled pen



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## Abstract

This prospective observational post-marketing survey aimed at studying the efficacy and convenience of the follitropin alpha filled-by-mass (FbM) pre-filled pen for patients in routine use. These data were analysed among 3196 non-selected treatment cycles and couples in seven Northern European countries. Valuable information was also obtained regarding the routine assisted reproduction treatment protocols used in Northern Europe. Out of 3196 cycles, human chorionic gonadotrophin (HCG) was administered in 3104 (97.2%), and an embryo transfer was carried out in 2766 cycles (86.5%). A positive HCG was recorded in 997 cycles (31.2% per started cycle and 36.0% per embryo transfer). The overall clinical pregnancy rate was 23.1% (738/3196) and per embryo transfer it was 26.7% (738/2766), with a miscarriage rate of 3.4% (95/2766) per embryo transfer or 9.5% (95/997) per positive HCG. Among the 732 elective single embryo transfers (eSET), the rate of positive HCG was 38.0% and the clinical pregnancy rate was 29.6%, suggesting that eSET is a valuable option in routine assisted reproduction. Although minor differences were observed between countries, the follitropin alpha FbM pre-filled pen proved clinically effective, was generally well tolerated, and both the women and nurses/midwives found the training easy.

**Keywords:** assisted reproduction, elective single embryo transfer, filled-by-mass, follicle stimulating hormone, follitropin alpha

## Introduction

The higher efficiency of recombinant human FSH (r-hFSH) in inducing pregnancies when compared with urinary FSH has been demonstrated in prospective randomized studies and meta-analyses (Bergh *et al.*, 1997; Daya and Gunby, 1999), even though this has not been shown in all analyses (van Wely *et al.*, 2003). A large database analysis in 2002, of 24,764 IVF/intracytoplasmic sperm injection (ICSI) cycles, also suggested the usefulness of r-hFSH in a non-selected population of patients (Ludwig *et al.*, 2004).

Using present recombinant manufacturing technologies, protein can be measured by mass, where a defined amount corresponds to its known biological activity (Driebergen and Baer, 2003; Hugues *et al.*, 2003; Balasch *et al.*, 2004). In the case of one

currently marketed r-hFSH product (follitropin alpha filled by mass; Gonal-f® FbM; Merck Serono International S.A., Geneva, Switzerland), 5.5 µg of the product corresponds to 75 IU. An observational study of follitropin alpha FbM as conventional injections without a pen among a non-selected population of 1427 IVF/ICSI patients in 21 units in the UK reported that it was efficacious and well tolerated (Lass *et al.*, 2004). In this large, non-selected group of couples, the ongoing clinical pregnancy rate per cycle was 23.1%, and 26.7% per embryo transfer.

The Gonal-f FbM pre-filled pen was introduced in Europe in 2004. In this post-marketing surveillance study, pregnancy results were evaluated after routine use of this pen in a large prospective observational study of 3196 non-selected IVF/ICSI

cycles in 81 IVF units in seven Northern European countries. Using questionnaires that were directed separately to couples and to midwives/nurses, the study also evaluated how easy the pre-filled pen was to use.

## Materials and methods

Eighty-one IVF units from seven countries participated in this study. Each unit recruited consecutive, non-selected patients who were eligible for IVF/ICSI with stimulation using the Gonal-f FbM pre-filled pen (Merck Serono International S.A.) during the period from August 2004 to November 2005. No patient inclusion or exclusion criteria were used. The study was approved by an ethics committee and all the participants gave informed consent.

The couples were given instructions on how to use the pen (with a 1.5 cm long 24-gauge needle) by midwives or nurses, and follitropin alpha FbM was then slowly self-administered. Two different questionnaires were used in this study. One was completed in the Netherlands, the UK and Ireland by the nurse/midwives (**Table 1**), and the other, with questions directed separately at the nurses/midwives and the couples, was used in the Nordic Countries (Denmark, Finland, Norway, and Sweden; **Tables 2 and 3**). The questions were related to the pen's ease of use and tolerability. The pre-filled pen was available containing 300, 450 or 900 IU doses, and the starting dose of r-hFSH was individualized per patient by healthcare providers at the clinics. The questionnaires were based on earlier comparable studies, but were made simpler (Bohannon *et al.*, 2000; Somkuti *et al.*, 2006).

The treatment was carried out according to the current practice in each clinic, using either gonadotrophin-releasing hormone (GnRH) agonists or antagonists for pituitary down-regulation. For luteal phase support, progesterone [Crinone® (micronized progesterone; Merck Serono International S.A.), Cyclogest (Actavis UK, Barnstaple, UK) or Lugesteron (Leiras, Turku, Finland)], vaginal micronized progesterone (Apotekarbolaget, Stockholm, Sweden) was given according to the prevailing routine in each country and clinic. In the Netherlands, HCG was also given.

A serum HCG pregnancy test was carried out 2–3 weeks after the embryo transfer. The clinical pregnancy was confirmed by ultrasound examination.

Data regarding patient demographics, stimulation characteristics, clinical outcomes including side effects, and embryology were collected for analysis.

## Statistics

Because this was an observational non-comparative study, the analysis consisted primarily of descriptive statistics. As is typical of observational trials, some data were missing from the collection forms. In this case, missing data were assumed to be of a random nature and no imputation of data was carried out. Therefore, all data presented are as reported, and summaries and percentages are on available data only. As a result, the number of reported observations may differ from one variable to another.

## Results

A total of 3196 cycles and couples were included in this study; of these, 666 were treated in Denmark, 425 in Finland, 299 in Norway, 481 in Sweden, 618 in the UK, 145 in Ireland and 562 in the Netherlands. Patient demographics, baseline characteristics and the causes of infertility are shown in **Table 4**. Briefly, male infertility was recorded in 43.8% of cases, while female infertility was recorded in 32.9% (1051/3196) of cases. Both a male and a female indication were present in 5.2% (166/3196) of cases, while 22.9% of cases were idiopathic. There were no differences in the distribution of female and male indications between the countries (data not shown).

Down-regulation was achieved using a GnRH agonist in 82.3% of cycles and a GnRH antagonist in 15.5% of cycles. The clinical pregnancy rate per agonist cycle was 24.2% (636/2631) and per antagonist cycle it was 19.2% (95/494). **Table 5** lists the doses of follitropin alpha FbM used.

Out of the 3196 cycles, HCG was given in 3104 (97.2%). An embryo transfer was carried out in 2766 cycles (86.5%). A positive HCG was recorded in 997 cycles (31.2% per started cycle and 36.0% per embryo transfer). The overall clinical pregnancy rate was 23.1% (738/3196) and per transfer it was 26.7% (738/2766), with a miscarriage rate of 3.4% (95/2766) per transfer or 9.5% (95/997) per positive HCG (**Table 6**). There were no differences in pregnancy rates when stratified by IVF or ICSI (data not shown).

In the Nordic countries, particularly in Sweden, a large proportion (66.0%, 291/441) of embryo transfers were elective single embryo transfers (eSET) (**Table 7**). For the whole study population 27.1% (732/2704) of cycles were eSET (**Table 7**).

The outcome of the cycles per number of transferred embryos is provided in **Table 7**. In this non-selected population, there were insignificant differences in the clinical pregnancy rates between eSET (29.6%) and transfer of two (27.0%) or three embryos (25.0%). If only one embryo was available for embryo transfer, the pregnancy rate was much lower (13.4%/embryo transfer). The incidence of ovarian hyperstimulation syndrome (OHSS; any grade) varied from 5.7% (42/732) in the eSET group to 0% (0/84) in the small three embryo transfer group, the average being 4.3% (**Table 6**). This reflects the selection of good prognosis patients for the eSET group.

The study also analysed the pregnancy rates per country, and the results are presented in **Table 8**. There were slight, although insignificant, differences for clinical pregnancy rate, with the highest rate occurring in Sweden (29.7%).

## Follitropin alpha FbM pre-filled pen questionnaire

The questionnaires addressed separately to the nurses/midwives and the patients in the Nordic centres showed that out of the 1730 women who answered, 1459 experienced the information given by the nurses/midwives as very easy to understand (1 or 2 on a scale of 1–10) (**Table 3**). Out of the 1807 women answering, 1553 regarded the pen as very easy and convenient to use (1 or 2 on a scale of 1–10) on the basis of the instructions. Only women

**Table 1.** Follitropin alpha filled by mass (FbM) pre-filled pen: patient comprehension and convenience, according to the questionnaires completed by the nurses/midwives in the British Isles and The Netherlands.

Question	British Isles (763 patients)	The Netherlands (562 patients)	Total (1325 patients)
<i>Training and experience</i>			
Has this patient had previous experience with daily injections?			
Yes	392 (51.4)	313 (55.7)	705 (53.2)
No	352 (46.1)	227 (40.4)	579 (43.7)
Missing	19 (2.5)	22 (3.9)	41 (3.1)
If yes, were these as part of an assisted reproduction cycle?			
Yes	374 (49.0)	308 (54.8)	682 (51.5)
No	73 (9.6)	35 (6.2)	108 (8.2)
Missing	316 (41.4)	219 (39.0)	535 (40.4)
During this cycle: who trained the patient to use the pre-filled pen?			
Doctor	3 (0.4)	17 (3.0)	20 (1.5)
Nurse	733 (96.1)	508 (90.4)	1241 (93.7)
Other	10 (1.3)	16 (2.8)	26 (2.0)
Missing	17 (2.2)	21 (3.7)	38 (2.9)
How long did the training take?			
0–15 min	589 (77.2)	498 (88.6)	1087 (82.0)
15–30 min	150 (19.7)	29 (5.2)	179 (13.5)
30–60 min	2 (0.3)	2 (0.4)	4 (0.3)
>60 min	1 (0.1)	1 (0.2)	2 (0.2)
Missing	21 (2.7)	32 (5.7)	53 (4.0)
<i>Patient comprehension</i>			
How did the patient find the training aspect of the pre-filled pen?			
Simple	497 (65.1)	412 (78.5)	909 (68.6)
Fairly simple	207 (27.1)	113 (21.5)	320 (24.2)
Difficult	13 (1.7)	12 (2.3)	25 (1.9)
Very difficult	0 (0.0)	0 (0.0)	0 (0.0)
Missing	46 (6.0)	5 (1.0)	51 (3.8)
Did the patient require more than one training session on how to use the pre-filled pen?			
Yes	65 (8.5)	41 (7.3)	106 (8.0)
No	629 (82.4)	494 (87.9)	1123 (84.8)
Missing	69 (9.0)	27 (4.8)	96 (7.2)
<i>Nurse feedback</i>			
How did you find the training of the patient to use the pre-filled pen?			
Simple	526 (68.9)	440 (78.3)	966 (72.9)
Fairly simple	167 (21.9)	60 (10.7)	227 (17.1)
Difficult	10 (1.3)	8 (1.4)	18 (1.4)
Very difficult	0 (0.0)	0 (0.0)	0 (0.0)
Missing	60 (7.9)	54 (9.6)	114 (8.6)

Values are number (percentage).

answered because they actually used the hormone. According to the answers of the nurses/midwives, 1279 women out of 1871 did not experience any adverse reactions to the pen (Table 2). In the UK and The Netherlands, the 1325 questionnaires answered by the nurses showed that the training of the patients was easy or relatively easy.

## Discussion

Follitropin alpha FbM in a pre-filled pen proved effective and easy for users in this large Northern European study of non-selected infertile couples.

On the basis of the questionnaires, training of the women to use these pre-filled devices proved simple. These results agree with those of a recent questionnaire study in which the same device was used for 61 women undergoing ovulation induction for oligoamenorrhoea who had used other gonadotrophin preparations during previous treatments (Somkuti *et al.*, 2006). Of the women who replied to the questionnaire in that study, 100% preferred the pre-filled pen to other preparations. The convenience of use of the pen was not directly measured in the present study, but in insulin users, a pen has resulted in better compliance (Bohannon *et al.*, 2000). The simplicity of the training as experienced by the women and medical staff supports this view.

**Table 2.** Follitropin alpha filled by mass (FbM) pre-filled pen: patient tolerability, according to the questionnaires completed by the nurses/midwives in the Nordic countries.

<i>Did the patient experience any adverse reaction to the pre-filled pen?</i>	<i>Nordic (1871 patients)</i>
Yes	544 (29.1)
No	1279 (68.4)
Missing	48 (2.6)

**Table 3.** Rating scale completed by the women treated in the Nordic countries (1 = very easy, 10 = very difficult).

<i>Rating</i>	<i>How did you experience the instruction from the nurse?</i>	<i>How did you experience the pre-filled pen in terms of convenience in administering?</i>
1	1103	1185
2	356	368
3	124	126
4	35	37
5	38	31
6	11	11
7	13	14
8	19	14
9	9	14
10	22	17
Missing	141	64

**Table 4.** Patient demographics, baseline characteristics and causes of infertility.

	<i>Pregnant (738 patients)</i>	<i>Not pregnant (2458 patients)</i>	<i>All (3196 patients)</i>	<i>British Isles (763 patients)</i>	<i>The Netherlands (562 patients)</i>	<i>Nordic (1871 patients)</i>
Age (years)						
Mean $\pm$ SD; range	32.8 $\pm$ 4.05; 21–43	34.0 $\pm$ 4.50; 19–46	33.7 $\pm$ 4.43; 19–46	34.4 $\pm$ 4.28; 21–46	34.2 $\pm$ 4.04; 23–43	33.3 $\pm$ 4.54; 19–45
No. $\geq$ 40	33	247	280	85	47	148
No. <40	704	2200	2904	678	513	1713
Missing	1	11	12	0	2	10
Body mass index <sup>a</sup>	24.9 $\pm$ 5.29; 17–55 (n = 416)	25.0 $\pm$ 5.58; 17–69 (n = 1331)	25.0 $\pm$ 5.51; 17–69 (n = 1747)	24.7 $\pm$ 4.06; 17–43 (n = 615)	26.5 $\pm$ 7.48; 17–69 (n = 492)	24.1 $\pm$ 4.63; 17–54 (n = 640)
Smoker (yes/no)	62/360	244/1151	306/1511	71/589	92/438	143/484
Cause of infertility n (%)						
Tubal factor	116 (15.7)	520 (21.2)	636 (19.9)	163 (21.4)	102 (18.1)	371 (19.8)
Unexplained	197 (26.7)	535 (21.8)	732 (22.9)	170 (22.3)	114 (20.3)	448 (23.9)
Dysovulation	63 (8.5)	158 (6.4)	221 (6.9)	36 (4.7)	18 (3.2)	167 (8.9)
Endometriosis	57 (7.7)	208 (8.5)	265 (8.3)	78 (10.2)	28 (5.0)	159 (8.5)
Male infertility	323 (43.8)	1077 (43.8)	1400 (43.8)	331 (43.4)	279 (49.6)	790 (42.2)
Other	61 (8.3)	192 (7.8)	253 (7.9)	69 (9.0)	50 (8.9)	134 (7.2)
Single cause	640 (86.7)	2091 (85.1)	2731 (85.5)	649 (85.1)	477 (84.9)	1605 (85.8)
More than one	87 (11.8)	291 (11.8)	378 (11.8)	98 (12.8)	57 (10.1)	223 (11.9)
No cause specified	11 (1.5)	76 (3.1)	87 (2.7)	16 (2.1)	28 (5.0)	43 (2.3)

<sup>a</sup>Mean  $\pm$  SD; range.

**Table 5.** Follitropin alpha filled-by-mass dose and duration of treatment.

	<i>Pregnant (738 patients)</i>	<i>Not pregnant (2458 patients)</i>	<i>All (3196 patients)</i>	<i>British Isles (763 patients)</i>	<i>The Netherlands (562 patients)</i>	<i>Nordic (1871 patients)</i>
Starting dose, IU	194 ± 78; 37.5–900 (n = 720)	222 ± 95; 37.5–1150 (n = 2371)	216 ± 92; 37.5–1150 (n = 3091)	229 ± 78; 75–460 (n = 758)	208 ± 96; 100–1150 (n = 543)	212 ± 96; 37.5–900 (n = 1790)
Days	11 ± 2.0; 2–20 (n = 721)	11 ± 2.3; 4–35 (n = 2364)	11 ± 2.2; 2–35 (n = 3085)	11.5 ± 2.3; 2–24 (n = 719)	11.0 ± 2.6; 5–21 (n = 515)	10.8 ± 2.0; 3–35 (n = 1851)
Total dose, IU	2158 ± 986; 337.5–11,700 (n = 707)	2503 ± 1251; 337.5–12,600 (n = 2317)	2423 ± 1203; 337.5–12,600 (n = 3024)	2641 ± 1065; 525–6750 (n = 726)	2333 ± 1190; 675–8850 (n = 516)	2359 ± 1249; 337.5–12,600 (n = 1782)

**Table 6.** Patient disposition and outcome.

	<i>British Isles (763 patients)</i>	<i>The Netherlands (562 patients)</i>	<i>Nordic (1871 patients)</i>	<i>All (3196 patients)</i>
HCG given	735 (96.3)	529 (94.1)	1840 (98.3)	3104 (97.2)
Embryo transfer performed	651 (85.3)	432 (76.9)	1683 (90.0)	2766 (86.5)
1 embryo	55 (8.4)	119 (27.5)	760 (45.2)	934 (33.8)
2 embryos	549 (84.3)	275 (63.7)	862 (51.2)	1686 (61.0)
3 embryos	25 (3.8)	7 (1.6)	52 (3.1)	84 (3.0)
Not specified	22 (3.4)	31 (7.2)	9 (0.5)	62 (2.2)
Positive HCG test	244 (32.0)	153 (27.2)	600 (32.1)	997 (31.2)
Clinical pregnancy	182 (23.9)	112 (19.9)	444 (23.7)	738 (23.1)
Biochemical pregnancy	32 (4.2)	19 (3.4)	71 (3.8)	122 (3.8)
Extrauterine pregnancy	5 (0.7)	3 (0.5)	12 (0.6)	20 (0.6)
Miscarriage	21 (2.8)	16 (2.8)	58 (3.1)	95 (3.0)
No information	4 (0.5)	3 (0.5)	15 (0.8)	22 (0.7)
Multiple pregnancy				
2 sacs	41 (100.0)	30 (93.8)	67 (98.5)	138 (97.9)
3 sacs	0 (0.0)	2 (6.3)	1 (1.5)	3 (2.1)
All	41/738 (5.6)	32/738 (4.3)	68/738 (9.2)	141/738 (19.1)
Ongoing at 7 weeks	–	–	433	–
1 fetus	–	–	375 (87.4)	–
2 fetuses	–	–	53 (12.4)	–
3 fetuses	–	–	1 (0.2)	–
OHSS	40 (5.2)	21 (3.7)	77 (4.1)	138 (4.3)
Mild	23 (57.5)	13 (61.9)	–	–
Moderate	9 (22.5)	6 (28.6)	–	–
Severe	7 (17.5)	2 (9.5)	–	–

HCG = human chorionic gonadotrophin; OHSS = ovarian hyperstimulation syndrome.

The overall rates of positive HCG and clinical pregnancy rate per cycle (31.2 and 23.1%) and per embryo transfer (36.0 and 26.7%) are no worse than those reported in the preliminary national statistics. The final statistics from the same period are not yet available. The drug preparation was generally well tolerated. The incidence of any grade of OHSS was highest among those who responded best to the stimulation (patients with eSET), and the overall rate (4.3%) was not high. This is all that can be said on the basis of the results of this observational study. Based on the Nordic questionnaire, patients and nurses/midwives found both

the instructions on how to use the follitropin alpha FbM pre-filled pen and the training procedure itself easy.

As well as this follitropin alpha FbM pre-filled pen, which is disposable, there is also a multi-use pen for follitropin beta on the market. The two pens were not compared in this study, so it is not possible to comment on possible differences in results when using them. The cost for the patient does not differ significantly, even though the pre-filled pen is less expensive in most countries. Although some patients might prefer a multi-use pen instead of

**Table 7.** Outcome by number of embryos transferred.

	<i>One embryo Elective (n = 732)</i>	<i>Compulsory<sup>a</sup> (n = 202)</i>	<i>Two embryos (n = 1686)</i>	<i>Three embryos (n = 84)</i>
Region				
British Isles	19	36	549	25
The Netherlands	71	48	275	7
Nordic	642	118	862	52
Country				
UK	18	34	448	13
Ireland	1	2	101	12
The Netherlands	71	48	275	7
Denmark	109	39	379	48
Finland	127	27	226	2
Norway	115	22	139	0
Sweden	291	30	118	2
Age (years)				
Mean $\pm$ SD (range)	32.5 $\pm$ 4.10 (19–44)	34.4 $\pm$ 4.67 (23–45)	33.8 $\pm$ 4.33 (21–45)	38.6 $\pm$ 3.85 (27–45)
$\geq 40$	22	24	135	48
<40	709	178	1543	36
Data missing	1	0	8	0
Positive HCG test (%)	278 (38.0)	41 (20.3)	622 (36.9)	30 (35.7)
Clinical pregnancy (%)	217 (29.6)	27 (13.4)	455 (27.0)	21 (25.0)
Multiple pregnancy				
2 sacs	3	0	127	4
3 sacs	0	0	3	0
OHSS (%)	42 (5.7)	3 (1.5)	67 (4.0)	0 (0)

Note: 62 patients had embryo transfer but no information on number transferred, so these patients are missing from this table.

<sup>a</sup>Only one embryo was available for transfer.

HCG = human chorionic gonadotrophin; OHSS = ovarian hyperstimulation syndrome.

**Table 8.** Clinical pregnancies by country.

<i>Country</i>	<i>Pregnant (738 patients)</i>	<i>Not pregnant (2458 patients)</i>	<i>All (3196 patients)</i>
UK	156 (25.2)	462 (74.8)	618
Ireland	26 (17.9)	119 (82.1)	145
The Netherlands	112 (19.9)	450 (80.1)	562
Denmark	159 (23.9)	507 (76.1)	666
Finland	78 (18.4)	347 (81.6)	425
Norway	64 (21.4)	235 (78.6)	299
Sweden	143 (29.7)	338 (70.3)	481

Values are n (%).

a disposable one, almost one-third of the patients in this study achieved a pregnancy, which means that they did not require a multi-use device. To obtain a final answer to this question, a prospective randomized study would be needed. In addition, the pre-filled pen reduces the possibility of any mistakes in dosing.

The observation that patients did not report pain may be due to the slow injection technique, with a very small needle and a simple to use device.

This post-marketing surveillance study provided valuable information on the treatment of infertility because it reflects routine clinical practice without the selection bias inherent to controlled, prospective randomized trials (Barlow, 2004; Lass and McVeigh, 2004). In addition to demonstrating the efficacy and safety of the follitropin alpha FbM pre-filled pen, the present report also revealed interesting details regarding the embryo transfer practice in IVF/ICSI cycles in Northern Europe. Some differences were observed between countries, but they are difficult to explain



on the basis of the collected data. The patient characteristics from country to country were quite similar, and the treatment itself did not differ significantly. No clear explanations can be given for these differences because the parameters that might explain them were not addressed in this study. What is common across this North European area is the low number of embryos transferred, and high numbers of embryos frozen. eSET did not result in lower pregnancy rates when compared with cycles in which two or three embryos were transferred. The pregnancy rates in this group were in fact higher than in groups with multiple embryos transferred. However, as expected, the pregnancy rates were lower in single embryo transfer cycles if only one embryo was available for transfer. The age of the small group of women ( $38.6 \pm 3.85$  years,  $n = 84$ ) who received three embryos was higher than that in the eSET group ( $32.5 \pm 4.10$  years). Age was obviously one of the criteria for transferring more than two embryos in countries where it is permissible to transfer multiple embryos. The results confirm those of an earlier, smaller survey in a non-selected population using eSET (Vilksa et al., 1999). No significant differences in pregnancy rates were found in prospective randomized trials regarding eSET versus double embryo transfer (Martikainen et al., 2001; Thurin et al., 2004; Gerris et al., 2005) carried out if good quality embryos existed. The proportion of women who were at least 40 years old in this survey was 8.8% and pregnancies were achieved among these patients, albeit at lower rates than younger patients. Women of this age are usually excluded from prospective randomized trials.

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*Declaration: Amir Lass declares that he was a Serono employee at the time of initiation of this study and during its early phase. The other authors report no financial or commercial conflicts of interest.*

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